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Effect of Selenium Supplements on Hemoglobin Concentration and Morbidity among HIV-1–Infected Tanzanian Women

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Abstract

Selenium deficiency may increase risks of anemia and morbidity among people with human immunodeficiency virus infection. We therefore investigated the effect of selenium supplements (200 µg of selenomethionine) on these end points among 915 pregnant Tanzanian women. Hemoglobin concentration was measured at baseline (at 12–27 weeks of gestation) and at 6 weeks and 6 months postpartum, and morbidity data were collected during monthly visits to the clinic. Selenium supplements had no effect on hemoglobin concentrations during follow-up (mean difference, 0.05 g/dL; 95% confidence interval, –0.07 to 0.16 g/dL) but reduced diarrheal morbidity risk by 40% (relative risk, 0.60; 95% confidence interval, 0.42–0.84). There was no effect on the other morbidity end points.

The trace element selenium may be a key nutrient during HIV infection. Low plasma selenium concentrations are related to increased risk of mortality [1] and mycobacterial disease [2] among people with HIV infection and are related to low hemoglobin concentrations among both HIV-infected and HIV-uninfected populations [3]. The apparently adverse consequences of selenium deficiency may be the result of the selenium requirement of antioxidant enzymes, such as glutathione peroxidase [4], which protect RBCs against oxidative damage [5].

The relationship between selenium and hemoglobin concentrations and infectious morbidity has not been studied adequately among persons with HIV infection in sub-Saharan Africa, even though nutritional deficiencies, infections, and anemia are common problems and are likely to

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interact in this geographic area. To address this research gap, we conducted a randomized, controlled trial of selenium supplements among HIV-1–infected Tanzanian women.

Methods

Participants in this study were adult female residents of Dar es Salaam, Tanzania, who were pregnant, between 12 and 27 weeks of gestation, and whose consent to HIV-1 testing led to a diagnosis of HIV-1 infection. In total, 915 women were recruited from September 2003 through July 2005 from prenatal clinics in Dar es Salaam and were followed up at a study clinic located at Muhimbili National Hospital in Dar es Salaam. Women were randomized to receive either a daily oral dose of 200 µg of elemental selenium (selenomethionine) in tablet form or placebo and were asked to take the regimen from enrollment until 6 months postpartum. The study protocol was approved by the institutional review boards at Muhimbili University of Health Sciences and Allied Sciences and the Harvard School of Public Health.

Participants received free standard prenatal and postnatal care at the study clinic. This included daily doses of ferrous sulphate (200 mg, equivalent to 60 mg ferrous iron) and folic acid (0.25 mg) during pregnancy. On the basis of prior findings [6], multivitamin supplements at multiples of the recommended dietary allowance were made available to study participants from the time of randomization until the time of delivery. A subset of patients were coenrolled in an efficacy trial comparing these vitamin dosages with lower dosages in line with the recommended dietary allowance. To prevent transmission of HIV from mother to child, treatment with nevi-rapine (200 mg) was made available to all women, and treatment with nevirapine (2 mg/kg) was made available to newborns within 72 h after delivery. HAART became available only toward the end of the study.

At baseline, trained research nurses obtained information on household socioeconomic status, education, obstetric history, anthropometric measures, and current health status. Nurses also obtained blood samples to measure immunological, virological, and hematological parameters, and study physicians performed a thorough clinical examination.

At each monthly follow-up visit to the clinic, participants were asked about the number of days, if any, on which they had experienced morbidity signs. Diarrhea was defined as ≥ 3 watery stools in the previous 24 h, and we asked whether mucus or blood was seen in the stool. Diarrheal episodes were classified as follows. “Acute diarrhea” was defined as a period of ≥ 1 day and < 14 days of diarrhea, and acute diarrhea was classified either as “dysentery,” which included all episodes of diarrhea with mucus or blood, or as “watery diarrhea,” which included episodes of diarrhea with neither mucus nor blood. There were few instances of “persistent diarrhea” (defined as ≥ 14 days of diarrhea), so this end point was not examined separately. Sufficient data were available on a limited set of other morbidities: cough, difficulty breathing, fatigue, fever, nausea or vomiting, ulcers in the mouth or throat, and oral thrush.

Hemoglobin concentrations were quantified using an AcT Diff II Analyzer (Beckman Coulter). T cell subset counts were measured with an FACSCCount system (Becton Dickinson), and plasma viral load was measured with an Amplicor HIV-1 Monitor Test (version 1.5; Roche Diagnostics).

The intention-to-treat principle was used for statistical analyses. General linear models for repeated measurements (PROC MIXED procedure in SAS, version 9.1; SAS Institute) were used to estimate mean differences in maternal hemoglobin concentrations. Point estimates of the change in values after randomization and 95% CIs directly modeled the difference between repeated measures. Cox proportional hazards regression models were used to model the effect of selenium supplements on the time to progression to hemoglobin concentration < 8.5 µg/dL.

The women eligible for these analyses had a baseline hemoglobin concentration ≥ 8.5 $\mu\text{g/dL}$ and at least 1 subsequent measurement of hemoglobin concentration.

To calculate the yearly number of maternal morbidity episodes, we multiplied the mean number of episodes per monthly visit by 12. Generalized estimating equations (PROC GENMOD procedure in SAS) with a working binomial distribution and a log link function were used to compare risks between treatment groups. Compliance with the study regimen was calculated by dividing the number of tablets absent from the returned bottles by the total number of tablets the participant should have taken.

Results

Of the 915 women who were randomized, 1 was excluded because of an invalid gestational age and 1 because she was found to be not pregnant. Of the remaining 913 women, 627 had baseline hemoglobin concentration data. Of these women, 531 also had data on hemoglobin concentration at 6 weeks postpartum, and 497 had data on hemoglobin concentration at 6 months postpartum. In total, 570 women with baseline samples also had at least 1 follow-up sample and morbidity data. These 570 women were similar to the women without hemoglobin measurements with regard to age, gestational age at study entry, years of schooling, gravidity, and mid-upper arm circumference.

Patients were enrolled in the study at a mean (\pm SD) of 21.6 ± 3.5 weeks of gestation, and the mean age was 27.7 ± 4.8 years. The mean CD4 cell count at baseline was 383 ± 225 cells/ μL , and the mean HIV-1 RNA load was 3.9 ± 0.9 \log_{10} copies/mL. There were no relevant differences in baseline characteristics between treatment groups. During follow-up, 31 women began HAART; of these 31 women, 17 were in the selenium supplement group and 14 were in the placebo group ($P = .53$). A total of 65 (11.4%) of the 570 women participated in a multivitamin equivalency trial, and participation did not differ between treatment groups ($P = .67$). Compliance with the study regimen was high (mean \pm SD, $91.6\% \pm 5.2\%$) and was similar between treatment groups ($P = .67$).

The mean hemoglobin concentration at baseline was 9.79 ± 1.28 g/dL in the selenium supplement group and 9.63 ± 1.44 g/dL in the placebo group ($P = .30$). The participants had a mean of 2.8 ± 0.4 samples available for hemoglobin measurement ($P = .70$). As expected, hemoglobin concentrations increased from baseline to the first postpartum visit (table 1). In analyses that were adjusted for baseline hemoglobin concentrations, selenium did not significantly increase hemoglobin concentrations during follow-up, compared with placebo (mean difference, 0.05 g/dL; 95% CI, -0.07 to 0.16 g/dL; $P = .73$).

A total of 467 women had baseline hemoglobin concentrations ≥ 8.5 g/dL with at least 1 follow-up measurement and were thus eligible for analyses that examined time to the progression to hemoglobin concentration < 8.5 g/dL. During the follow-up of mean duration of 9.3 ± 1.9 months, 15 women progressed to hemoglobin concentration < 8.5 g/dL. Selenium did not affect the risk of progression (hazard ratio, 0.62; 95% CI, 0.22–1.74).

We next examined the effect of selenium supplements on morbidity during follow-up (table 2). Selenium supplements reduced the risk of overall diarrheal-related morbidity (defined as acute or persistent diarrhea) by 40% (relative risk, 0.60; 95% CI, 0.42–0.84). Selenium supplements also significantly reduced risks of acute diarrhea (relative risk, 0.59; 95% CI, 0.42–0.83) and watery diarrhea (relative risk, 0.56; 95% CI, 0.39–0.81). There was no effect on other morbidity end points.

Discussion

In this randomized trial involving HIV-1–infected pregnant women, selenium supplements had no effect on maternal hemoglobin concentrations. The supplements decreased diarrheal morbidity but had no effect on other morbidities.

Observational studies implicate biochemical selenium deficiency in the etiology of anemia [7,8]. Among adults from Malawi with pulmonary tuberculosis, selenium concentrations were inversely related to hemoglobin concentrations among HIV-infected and HIV-uninfected groups [3]. Laboratory studies show that selenium, as part of glutathione peroxidases, protects against hemolysis of erythrocytes and thus may be relevant to hemoglobin levels [5]. However, our findings do not support a role for selenium in the maintenance of hemoglobin concentrations and in the prevention of anemia among HIV-1–infected adults in our setting.

Selenium supplements decreased the risk of diarrheal morbidity, which in this study cohort was mostly caused by acute diarrhea, especially the watery type. To our knowledge, this is the first evidence from a selenium trial on the prevention of morbidities among persons with HIV infection.

The effect may be explained by the link between selenium and improved defense against oxidative stress, which may limit hypersecretion in the small intestine [9]. The effect is unlikely to have been mediated through effects on concentrations of T cells or HIV-1 RNA load [10]. The selenium supplements did not have an effect on morbidities other than diarrhea. In contrast, selenium use decreased hospital admissions among adults from Miami, Florida [11].

The effect of selenium supplements in this study may have been limited by a potentially low prevalence of selenium deficiency in the study population. In a comparable population, plasma selenium concentrations (mean \pm SD, 124 ± 22 μ g/L) were not indicative of widespread selenium deficiency [1], possibly because of consumption of seafood or other high selenium–containing foods. Alternatively, the dosage of selenium used in the current study may have been too low. However, this explanation is unlikely, because the dose represents ~ 3 times the recommended dietary allowance during pregnancy and lactation [12]. The study is also limited by the fact that it relies on patient recall of morbidities, which may lead to misclassification. However, this misclassification is likely to be non-differential, and we were nevertheless able to detect differences between treatment groups in diarrheal morbidity.

In conclusion, 200 μ g of selenium taken daily from 12–27 weeks of gestation until 6 months postpartum did not have an effect on hemoglobin concentrations among HIV-1–infected Tanzanian women but decreased the risk of diarrheal morbidity. The findings on decreased diarrheal morbidity are encouraging and merit further study; however, our results do not support a large beneficial role for selenium supplements for women with HIV infection in coastal sub-Saharan Africa.

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References

1. Kupka R, Msamanga GI, Spiegelman D, et al. Selenium status is associated with accelerated HIV disease progression among HIV-1-infected pregnant women in Tanzania. *J Nutr* 2004;134:2556–2560. [PubMed: 15465747]

2. Shor-Posner G, Miguez MJ, Pineda LM, et al. Impact of selenium status on the pathogenesis of mycobacterial disease in HIV-1-infected drug users during the era of highly active antiretroviral therapy. *J Acquir Immune Defic Syndr* 2002;29:169–173. [PubMed: 11832687]
3. van Lettow M, West CE, van der Meer JW, Wieringa FT, Semba RD. Low plasma selenium concentrations, high plasma human immunodeficiency virus load and high interleukin-6 concentrations are risk factors associated with anemia in adults presenting with pulmonary tuberculosis in Zomba district, Malawi. *Eur J Clin Nutr* 2005;59:526–532. [PubMed: 15741985]
4. Flohe L. Glutathione peroxidase. *Basic Life Sci* 1988;49:663–668. [PubMed: 3074794]
5. Rotruck JT, Pope AL, Ganther HE, Hoekstra WG. Prevention of oxidative damage to rat erythrocytes by dietary selenium. *J Nutr* 1972;102:689–696. [PubMed: 5022203]
6. Fawzi WW, Msamanga GI, Spiegelman D, et al. Randomised trial of effects of vitamin supplements on pregnancy outcomes and T cell counts in HIV-1-infected women in Tanzania. *Lancet* 1998;351:1477–1482. [PubMed: 9605804]
7. Semba RD, Ferrucci L, Cappola AR, et al. Low serum selenium is associated with anemia among older women living in the community: the women's health and aging studies I and II. *Biol Trace Elem Res* 2006;112:97–107. [PubMed: 17028376]
8. Van Nhien N, Khan NC, Yabutani T, et al. Serum levels of trace elements and iron-deficiency anemia in adult Vietnamese. *Biol Trace Elem Res* 2006;111:1–9. [PubMed: 16943592]
9. Lindley KJ, Goss-Sampson MA, Muller DP, Milla PJ. Lipid peroxidation and electrogenic ion transport in the jejunum of the vitamin E deficient rat. *Gut* 1994;35:34–39. [PubMed: 8307446]
10. Kupka R, Mugusi F, Aboud S, et al. Randomized, double-blind, placebo- controlled trial of selenium supplements among HIV-infected pregnant women in Tanzania: effects on maternal and child outcomes. *Am J Clin Nutr* 2008;87:1802–1808. [PubMed: 18541571]
11. Burbano X, Miguez-Burbano MJ, McCollister K, et al. Impact of a selenium chemoprevention clinical trial on hospital admissions of HIV-infected participants. *HIV Clin Trials* 2002;3:483–491. [PubMed: 12501132]
12. Food and Nutrition Board. DRI: dietary reference intakes for vitamin C, vitamin E, selenium, and carotenoids. Washington, DC: National Academy Press; 2000.

Table 1

Effect of selenium supplements on hemoglobin concentrations in HIV-1–infected pregnant women.

| End point | Selenium supplement group | | | Placebo group | | | P |
|--|---------------------------|--------------|---------------------|-----------------------------------|---------------|--------------|-----------------------|
| | No. of events | No. of women | Mean value \pm SD | Hazard ratio (95% CI) | No. of events | No. of women | Hazard ratio (95% CI) |
| Hemoglobin concentration, g/dL | | | | | | | |
| Baseline | ... | 284 | 9.79 \pm 1.28 | ... | ... | 286 | 9.63 \pm 1.44 |
| At 6 weeks postpartum | ... | 264 | 11.51 \pm 1.56 | ... | ... | 267 | 11.40 \pm 1.55 |
| At 6 months postpartum | ... | 250 | 11.49 \pm 1.33 | ... | ... | 247 | 11.35 \pm 1.55 |
| Mean difference, g/dL | ... | ... | ... | 0.05 (–0.07 to 0.16) ^d | ... | ... | Reference |
| Progression to hemoglobin concentration <8.5 g/dL ^c | 6 | 241 | ... | 0.62 (0.22–1.74) ^d | 9 | 226 | Reference |

^a Point estimates and 95% CIs directly modeled the differences between repeated measures.

^b P value obtained from a robust parallel-groups analysis with adjustment for baseline.

^c Among women with baseline hemoglobin concentration \geq 8.5 g/dL and at least 1 follow-up measurement of hemoglobin concentration.

^d Calculated using Cox proportional hazards regression model.

Table 2

Effect of selenium supplements on morbidity in HIV-1-infected pregnant women.

| Symptom | Morbidity rate, episodes/year ^a | Relative risk (95% CI) ^b | <i>P</i> ^b |
|---------------------------|---|-------------------------------------|-----------------------|
| Diarrhea | | | |
| All | 0.48 | 0.60 (0.42–0.84) | .003 |
| Acute | 0.47 | 0.59 (0.42–0.83) | .003 |
| Watery | 0.36 | 0.56 (0.39–0.81) | .002 |
| Dysenteric | 0.13 | 0.56 (0.26–1.19) | .13 |
| Cough | 1.45 | 0.95 (0.77–1.18) | .65 |
| Difficulty breathing | 0.17 | 1.30 (0.75–2.24) | .36 |
| Fatigue | 0.28 | 1.26 (0.83–1.92) | .28 |
| Fever | 0.71 | 0.73 (0.44–1.20) | .22 |
| Nausea or vomiting | 0.17 | 1.20 (0.70–2.07) | .51 |
| Ulcers in mouth or throat | 0.20 | 1.30 (0.74–2.30) | .36 |
| Oral thrush | 0.08 | 1.02 (0.40–2.58) | .97 |

NOTE. Morbidity data were available for all 570 women. During follow-up, 5016 measurements were taken.^a Mean number of episodes per monthly visit times 12.^b Calculated from generalized estimating equations with a working binomial distribution and a log link function.